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Pharma Fights Back: Combating Heightened Prosecution of Off-Label Promotion with Claims of First Amendment Violations

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Abstract: The FD&C Act and FDA-promulgated regulations work together to bar off-label promotion by pharmaceutical companies. This regulatory framework is often confusing and ambiguous, and FDA "guidance" on the issue has done relatively little to provide clarity. There was a series of trials and appeals in the late 1990s on the constitutionality of such speech restrictions, in which the plaintiff claimed that by prohibiting commercial speech, the First Amendment rights of pharmaceutical companies were being violated. But ultimately confusion perpetuated: although the cases culminated in an injunction against the FDA, the agency reinterpreted their guidance as merely safe harbors that provided no independent prosecutorial basis, rendering the court's injunction moot. Prosecution of pharmaceutical companies for off-label promotion has increased over the past five years; recently, some pharmaceutical companies have responded by raising anew the First Amendment claims of a decade ago. This time, however, the claims are more narrowly focused, and if the recent oral arguments in front of the Second Circuit are any indication, carry a strong chance of winning.

I. Introduction

Prosecution of pharmaceutical companies for promoting applications of their drugs that have not received FDA approval—known as off-label promotion—has skyrocketed in recent years, both in terms of number of cases and penalties handed out.¹ Earlier this year, the FDA changed their internal regulations to give agency members more freedom to pursue criminal investigations.² The FDA also delineated a specific roadmap for initiating criminal prosecutions of senior company officials under the Park Doctrine.³ Despite these heavy potential sanctions, the underlying statutory and regulatory scheme is a morass of ambiguity, comprised mainly of FDA regulations promulgated under the Food, Drug, and Cosmetic Act (FD&C Act), which itself does not prohibit off-label promotion. Recently, some of the companies being investigated by the FDA have responded by challenging the constitutionality of these rules. The crux of the claim is that speaking about off-label uses for their own products constitutes commercial free speech, and while some limits can admittedly be applied, the prohibitions in place are so broad that they violate the plaintiffs' First Amendment rights. The D.C. Circuit saw a string of litigation on these constitutional issues in the late 1990s, with inconclusive results.⁴ In the past year and a half, two major cases have been filed against the United States,⁵ with one currently pending before the Second Circuit. If the court finds that the FDA has restricted commercial speech too broadly in off-label promotion situations, it could trigger a major change in the FDA's approach to prosecuting these violations.

¹ SAMMY ALMASHAT ET AL., RAPIDLY INCREASING CRIMINAL AND CIVIL MONETARY PENALTIES AGAINST THE PHARMACEUTICAL INDUSTRY: 1991–2010 at 2 (2010).

² JOHN T. BENTIVOGLIO & JENNIFER L. BRAGG, FDA REVAMPS CRIMINAL PROSECUTION GUIDELINES AND EXPANDS HEALTH CARE FRAUD-RELATED INVESTIGATIONS 2 (2011), *available at* http://www.skadden.com/newsletters/FDA_Revamps_Criminal_Prosecution_Guidelines.pdf.

³ *Id.* at 3.

⁴ See *Washington Legal Foundation v. Henney*, 128 F.Supp.2d 11 (D.D.C. 2000).

⁵ However, one suit was subsequently withdrawn as part of a settlement agreement with the Department of Justice.

II. Evolution of the Current Regulatory Structure

The FD&C Act grants the FDA the authority to regulate promotional material put forth by drug and device manufacturers about their products. Over eighty percent of promotional spending by pharmaceutical companies is directed at physicians,⁶ making this channel of communication a major area of focus for the FDA. One particular area of concern is when pharmaceutical companies provide information to physicians about the use of their product in situations other than those that have been approved by the FDA. Physicians are allowed to prescribe a drug for an off-label use,⁷ and in fact off-label use has become the standard of care for some patients, with providers receiving reimbursement through Medicare or Medicaid.⁸ Yet companies still face stringent restrictions in their dissemination of materials to physicians regarding these off-label uses. The FD&C Act does not explicitly prohibit off-label promotion, but the FDA has interpreted it to fall under the broad prohibitions against false or misleading advertising and introduction of a drug into interstate commerce without FDA approval for all of its intended uses.⁹

Labeling on FDA-approved drugs is prohibited from being “false or misleading in any particular.”¹⁰ Labeling is defined broadly in the FD&C Act to include all labels and written material on or accompanying a product.¹¹ The Supreme Court in 1948 created a broad reading of

⁶ *Regulating Prescription Drug Promotion*, 108th Cong. (2003), (statement of Janet Woodcock, Director, Center for Drug Evaluation and Research), available at <http://www.fda.gov/NewsEvents/Testimony/ucm115080.htm>.

⁷ Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the Food and Drug Administration: Notice of Proposed Rulemaking 37 Fed. Reg. 16503 (August 15, 1972) (to be codified at 21 C.F.R. pt. 130).

⁸ See, e.g., Medicare and Medicaid Programs; Conditions for Coverage for End-Stage Renal Disease Facilities, 73 Fed. Reg. 20370, 20375 (Dep’t of Health and Human Services April 15, 2008) (final rule).

⁹ Michelle Mello et al., *Shifting Terrain in the Regulation of Off-Label Promotion of Pharmaceuticals*, New England Journal of Med., 360 NEW ENG. J. MED. 1557, 1558 (2009); see also Defendants’ Memorandum of Points and Authorities In Support of Motion to Dismiss or For Summary Judgment at 6, *Allergan, Inc. v. United States of America et al.*, No. 09-1879.

¹⁰ 21 U.S.C. § 352(a) (2007).

¹¹ 21 U.S.C. § 321(m) (2009).

“accompanying,” such that the “textual relationship” between the product and the information is the determinative factor, regardless of the geographic or temporal distance between the two.¹² Through regulations, the FDA has expanded the definition of labeling to its conceptual outer bounds, and “labeling” now encompasses everything from price lists and motion picture films to scientific journals and reference texts.¹³ In contrast to the FD&C Act, on its face the FDA regulatory framework no longer explicitly require that material “accompany” a drug in order to be considered labeling.¹⁴ A drug’s labeling may not imply a use other than those approved by the FDA; if the labeling does so, it becomes false and misleading in contravention of the FD&C Act.¹⁵ Because the definition of “labeling” encompasses so many forms of communications from a drug manufacturer, it becomes easy for a pharmaceutical company to create a false or misleading label through truthful statements about their product’s off-label uses.¹⁶

The second, related prohibition against off-label promotion stems from inadequate directions for use.¹⁷ Since 1962, manufacturers must obtain premarket approval for any new drug they wish to sell.¹⁸ To obtain approval, the producer must show that the drug is “safe and effective for each of its intended uses.”¹⁹ According to the FDA, if a drug takes on a new intended use, then it becomes a new drug, and the producer must prove the drug is safe and

¹² *Kordel v. United States*, 335 U.S. 345, 350 (1948).

¹³ 21 C.F.R. § 202.1(l)(2) (2008).

¹⁴ See 21 U.S.C. § 355(a) (2010); § 321(p) (2009); § 21 C.F.R. § 202.1(l)(2) (2008).

¹⁵ See e.g., *Washington Legal Foundation v. Friedman*, 13 F. Supp. 2d 51, 67 (D.D.C. 1998); John Osborn, *Can I Tell You the Truth? A Comparative Perspective on Regulating Off-Label Scientific and Medical Information*, 10 YALE J. HEALTH POL’Y L. & ETHICS 299, 308 (2010).

¹⁶ Osborn, *supra* note 10, at 308.

¹⁷ Specific Requirements on Content and format of Labeling for Human Prescription Drugs; Revision of “Pediatric Use” Subsection in the Labeling, 59 Fed. Reg. 64240, 64243 (Dec. 13, 1994) (to be codified at 21 C.F.R. pt. 201).

¹⁸ 21 U.S.C. § 331(d) (2009); 21 U.S.C. § 355(a) (2010); see also Defendants’ Memorandum of Points and Authorities In Support of Motion to Dismiss or For Summary Judgment, *supra* note 4, at 2–3.

¹⁹ Defendants’ Memorandum of Points and Authorities In Support of Motion to Dismiss or For Summary Judgment, *supra* note 4, at 3.

effective for that new use.²⁰ A substance falls under the purview of the FDA as a drug if it is “intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals.”²¹ The FDA adopts a broad view of “intended use,” looking at the objective intent of the producer, as shown by labeling claims, advertising, or oral or written statements by the company.²² Thus, if a drug manufacturer, through promotional claims about its products, makes a statement regarding a drug’s efficacy in an off-label use, then the off-label use becomes a statutory “intended use,” triggering the required proof of safety and efficacy.²³ Failure to include FDA-approved information about this new use on the label is misbranding.²⁴

If a pharmaceutical company provides information to a physician in response to an unsolicited request, the FDA will not subject these communications to the requirements of the FD&C Act.²⁵ But when pharmaceutical companies instigate contact with physicians, the FDA may exert its regulatory authority.²⁶ Because the FD&C Act does not explicitly forbid off-label promotion, the line separating advertising and labeling that does fall under the Act’s strictures from statements that do not has generally been formed through FDA-issued “guidance”²⁷ and case law. During the 1990s, under the leadership of Dr. David Kessler, the FDA heightened its

²⁰ *Id.* at 5.

²¹ 21 U.S.C. § 321(g) (2009).

²² 21 C.F.R. § 201.128 (1976).

²³ Guidance for Industry on Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices, 74 Fed. Reg. 1694 (Jan. 13, 2009) (notice), *available at* <http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm>; *see also* Osborn, *supra* note 10, at 309–11.

²⁴ Citizen Petition Regarding the Food and Drug Administration’s Policy on Promotion of Unapproved Uses of Approved Drugs and Devices, 59 Fed. Reg. 59820, 59822 (Nov. 18, 1994) (notice).

²⁵ *Id.* at 59823.

²⁶ *Id.*

²⁷ According to the FDA, guidance represents the agency’s “current thinking” on a topic, but does not “create or confer any rights” and is binding on neither the agency nor the regulated party. Advertising and Promotion; Guidances, 61 Fed. Reg. 52800, 52801 (Oct. 8, 1996) (notice).

attention toward off-label use and promotion.²⁸ In the early 1990s, the FDA began, for the first time, to regulate the dissemination of literature by drug and device manufacturers if such materials discussed off-label uses.²⁹ The FDA's policies in this area initially took the form of ad hoc, individual warning letters; the agency subsequently created more formal guidance documents.³⁰

In 1992, the FDA introduced guidance describing the types of pharmaceutical-supported scientific and educational activities (such as continuing medical education seminars) that would be subject to the FD&C Act.³¹ Five years later, after notice and comment, the FDA issued a final version of the guidance.³² The FDA expressed concern that their policies would stifle academic discussion, which is why the agency explained that communications “independent of the promotional influence” of the manufacturer of the product at issue would not fall under the FD&C Act's requirements, even if such communications discussed off-label uses for a drug.³³ To make a determination of independence, the FDA would focus on a variety of factors, such as the extent to which the producer is able to use its presentation as an advertising mechanism,³⁴ and the opportunity for meaningful discussion about the product.³⁵

In 1996, the FDA expanded their guidance to reference texts and medical journal articles distributed by members of the pharmaceutical industry.³⁶ The FDA explicitly allowed pharmaceutical companies to circulate copies of journal articles about their products, as long as certain factors were met, most notably the “principle subject” of the articles must be FDA-

²⁸ Osborn, *supra* note 10, at n.36.

²⁹ Washington Legal Foundation v. Friedman, 36 F.Supp.2d 16, 19 (D.D.C. 1999).

³⁰ *Id.*

³¹ Draft Policy Statement on Industry Supported Scientific and Educational Activities, 57 Fed. Reg. 56412 (Nov. 27, 1992) (notice).

³² Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64074 (Dec. 3, 1997).

³³ Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. at 64076.

³⁴ Draft Policy Statement on Industry Supported Scientific and Educational Activities, 57 Fed. Reg. at 56413–14.

³⁵ Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. at 64087.

³⁶ Advertising and Promotion; Guidances, 61 Fed. Reg. 52800 (Oct. 8, 1996) (notice).

approved uses for the products, and there must be a clear notification to the reader that the off-label uses are unapproved.³⁷ Reference texts that are written and published “independent of the commercial interest” of the producer of the drug at issue may be distributed by that producer, as long as the listed requirements are met.³⁸ The reference text should not “have a significant focus” on unapproved uses of drugs produced by the firm distributing the materials, and if such information does play a minor role in the text, a company’s representatives are directed not to “refer to, or otherwise promote . . . information in the reference text that is not consistent” with the product’s FDA-approved labeling.³⁹

In 1997, Congress joined the conversation when they passed the FDA Modernization Act (FDAMA), modifying the FD&C Act.⁴⁰ The FDAMA allowed pharmaceutical companies to distribute information regarding off-label uses to physicians, insurance companies, and government agencies, as long as six factors were met:

“(1) the drug was approved, (2) the information was not false or misleading; did not otherwise render the drug misbranded, was in the form of an unabridged reprint from a peer-review journal or reference publication, and would not pose a significant risk to public health, (3) the information was not derived from another manufacturer’s research (absent permission), (4) the manufacturer submitted the information to FDA 60 days before its distribution, (5) the manufacturer had submitted a supplemental NDA to FDA for approval of the use described (or certified that a supplemental NDA would be submitted within six months), and (6) the reprint included a prominent statement that the use had not been approved, [along with] a copy of the approved labeling.”⁴¹

³⁷ Advertising and Promotion; Guidances, 61 Fed. Reg. at 52801.

³⁸ *Id.*

³⁹ *Id.*

⁴⁰ FDA.com, Food, Drug, and Modernization Act (FDAMA) of 1997, <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendments/totheFDCA/FDAMA/default.htm> (last visited February 20, 2011). The FDA promulgated implementing regulations the next year. Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices, 21 C.F.R. 99 (2011) (final rule).

⁴¹ PETER BARTON HUTT ET AL., FOOD AND DRUG LAW: CASES AND MATERIALS 549 (Thomson Reuters/Foundation Press 2007) (1980).

The FDAMA provisions applied to scientific journals and texts, but did not mention CME seminars. Few pharmaceutical companies took advantage of the Act's mechanism for distributing off-label information.⁴² The requirement that a manufacturer submit or commit to submitting a supplemental NDA for the off-label use entailed clinical trial expenses many companies were not interested in incurring. Some of Congress's other proposals took a more permissive attitude toward off-label use and promotion, but the FDA met these suggestions with hostility. For example, Senate bill 1477 would have created a special mechanism for FDA approval of new (off-label) uses for current drugs if the off-label use was practiced for five years, was "common" among physicians, and was "reasonable" based on existing experience and evidence.⁴³ Dr. Kessler blasted the proposition as one that would create a gaping hole in the current requirement to prove a new drug's effectiveness, returning the FDA to the pre-1962 era of drug regulation.⁴⁴

The FDAMA lapsed on September 30, 2006, and was not replaced by new legislation on the subject.⁴⁵ In 2008, the FDA posted notice of proposed guidance on the issue of distribution by drug and device manufacturers of scientific journals and texts that discuss off-label uses of their products.⁴⁶ The final version of the FDA's "current thinking on 'Good Reprint Practices'" was released in January of 2009.⁴⁷ If a manufacturer follows these guidelines, the FDA "does

⁴² *Id.*

⁴³ Protecting and Promoting Public Health: Hearing on S. 1477 Before the S. Comm. on Labor and Human Resources, 104th Cong. (1996) (statement of Dr. David A. Kessler, Comm'r, FDA), *available at* <http://www.fda.gov/NewsEvents/Testimony/ucm115101.htm>.

⁴⁴ *Id.*

⁴⁵ PETER BARTON HUTT ET AL., *FOOD AND DRUG LAW: CASES AND MATERIALS* 549 (Thomson Reuters/Foundation Press 2007) (1980).

⁴⁶ Draft Guidance for Industry on Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices, 73 Fed. Reg. 9342 (Feb. 20, 2008) (notice).

⁴⁷ Guidance for Industry on Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices, 74 Fed. Reg. 1694-01 (Jan. 13, 2009) (notice), *available at* <http://www.fda.gov/oc/op/goodreprint.html>.

not intend” to consider the distribution of articles and texts discussing off-label uses as creating a new and unapproved “intended use.”⁴⁸ There are many similarities between the 2009 guidance and the FDAMA, such as restrictions on whom information can be disseminated to, and disclosure requirements about the distributor’s interest in the product and the unapproved nature of the use.⁴⁹ However in other respects, the 2009 guidance is more lenient than its predecessor. For example, while the FDAMA required a pharmaceutical company to submit or commit to submitting a supplemental NDA for the off-label use its literature was discussing, the new guidance does not mention requirements for a supplemental NDA.⁵⁰ The FDAMA mandated that any literature discussing off-label uses be submitted to the FDA 60 days before distribution; the 2009 guidance is again silent on such notification.⁵¹ Under the FDAMA regime, the clinical data underlying articles or texts was not allowed to originate from another company’s research, absent explicit permission.⁵² The 2009 guidance allows any “adequate and well-controlled clinical studies” that were published in a medical journal or text to serve as the basis for materials the company distributes.⁵³ However, unlike the FDAMA, the guidance creates no explicit safe harbor for pharmaceutical companies, and thus complying with the FDA’s suggestions does not prevent possible liability.

Some challenged the FDA’s recent guidance as overly permissive. In a letter to FDA Commissioner Andrew Eschenbach, Henry Waxman, Chairman of the House Committee on Oversight and Government Reform, blasted the guidance for “undercutting” the traditional

⁴⁸ *Id.*

⁴⁹ Michelle Mello et al., *Shifting Terrain in the Regulation of Off-Label Promotion of Pharmaceuticals*, New England Journal of Med., 360 NEW ENG. J. MED. 1557, 1560 (2009)

⁵⁰ *Id.*

⁵¹ *Id.*

⁵² *Id.*

⁵³ Guidance for Industry on Good Reprint Practices, 74 Fed. Reg. 1694-01.

prohibition on off-label promotion.⁵⁴ Judy Cahill, Executive Director of the Academy of Managed Care Pharmacy, complained that the FDA's new unofficial rules were insufficient to protect against dissemination of biased research, which could create mistaken beliefs among healthcare providers about the efficacy of off-label uses.⁵⁵ Others praised the guidance for allowing drug producers to close the information gap that can result during the often long delays for drug approval, during which time a company is aware of a trend of successful off-label use, but would otherwise face constraints on sharing this information with physicians.⁵⁶ One example cited by supporters of the new guidance is Herceptin, a drug produced by Genentech that decreases the chance of breast cancer relapse.⁵⁷ It was not until two years after studies indicated its efficacy that the drug was approved for this use by the FDA.⁵⁸ During the intervening time, many physicians did not prescribe the drug, to the potential detriment of many patients.⁵⁹ Genentech blamed the delayed adoption of Genentech on their inability to circulate information about its efficacy to physicians.⁶⁰

III. Initial Challenges to the Constitutionality of FDA Regulation of Off-Label Promotion

Washington Legal Foundation (WLF), a non-profit organization that engages in litigation to support the free market,⁶¹ took the lead in challenging the constitutionality of the FDA's

⁵⁴ Henry Waxman, Chairman of House Committee on Oversight and Government Reform, letter to Andrew Eschenbach, Food and Drug Administration Commissioner. Nov. 30, 2007.

⁵⁵ Stephen Barlas, New FDA Guidance on Off-Label Promotion Falls Short for Everyone. *Pharmacy and Therapeutics*, Vol. 34, No. 3, 122–23 (March 2009).

⁵⁶ Scott Hensley, *FDA's "Off-Label" Promotion Notion: 'Good Framework' vs. 'Fantasy'*, WSJ Health Blog, April 25, 2008, <http://blogs.wsj.com/health/2008/04/25/fdas-off-label-promotion-notion-good-framework-v-fantasy/>.

⁵⁷ *Id.*

⁵⁸ *Id.*

⁵⁹ *Id.*

⁶⁰ *Id.*

⁶¹ wlf.org, WLF Mission, <http://www.wlf.org/org/mission.asp> (last visited Feb. 20, 2011).

regulation of off-label promotion. In 1998, in the District Court of the District of Columbia, WLF embarked upon the first round of what would be a multi-year battle with the FDA.⁶² WLF argued the FDA's 1996 and 1997 guidance documents were unconstitutional because, in restricting manufacturer promotion of off-label uses, they violated the First Amendment's protection of commercial speech.⁶³ The FDA tried to claim that promotional activities are conduct, not speech, a notion the court swiftly dismissed.⁶⁴ As the court noted, drug and device labeling issues have been consistently analyzed, not as conduct, but under the framework of commercial speech.⁶⁵ Commercial speech is generally defined as speech by a commercial entity "that wishes to financially benefit from the message."⁶⁶ Just as quickly, the court rejected the FDA's assertion that, because of their broad power to regulate in the field of prescription drugs, the government could restrict commercial speech without running afoul of the First Amendment.⁶⁷ Resigned to defending the restrictions as acceptable limitations on commercial speech, the FDA had to prove their policies passed the *Central Hudson* commercial speech test.⁶⁸ Under *Central Hudson*, commercial speech can be constrained if the speech is unlawful or inherently misleading, or alternately, if the government has a substantial interest achieved by the regulations, the interest is directly advanced by the restrictions, and the restrictions are not substantially more restrictive than necessary (however, using the least restrictive means available is not required).⁶⁹

⁶² Washington Legal Foundation v. Friedman, 13 F. Supp. 2d 51 (D.D.C. 1998).

⁶³ *Id.* at 54.

⁶⁴ *Id.* at 59.

⁶⁵ *Id.* at 62.

⁶⁶ *Id.*

⁶⁷ *Id.* at 60–61 (citing 44 Liquormart, Inc. v. Rhode Island, 517 U.S. 484, 512 (1996)).

⁶⁸ *Id.* at 65.

⁶⁹ Central Hudson Gas & Elec. Corp. v. Public Service Commission of New York, 447 U.S. 557, 566 (1980).

With respect to the first factor, the FDA argued the speech did involve illegal activities, and thus could be restricted, because promoting an off-label use renders the drug misbranded, in violation of the FD&C Act. The court rejected this argument, explaining that the crux of the inquiry is not whether the commercial speech itself violates a law (as the FDA was implying), but instead whether the behavior promoted by the speech is unlawful.⁷⁰ Because physicians can legally prescribe drugs for off-label uses, the commercial speech encourages a lawful activity.⁷¹ While the first half of this prong of *Central Hudson* was not a close call for the court, the inquiry into whether the commercial speech was misleading entailed a more detailed analysis.

“Inherently misleading” is a high bar, and speech that simply may be misleading in some circumstances is not sufficient to remove the speech from *Central Hudson* analysis.⁷² Although the FDA asserted in their motion for summary judgment that off-label promotion is inherently misleading,⁷³ in the very guidance documents at issue, they had previously described such statements as only “potentially misleading.”⁷⁴ According to the court, “the FDA was right the first time.”⁷⁵ Simply because a researcher publishes a claim in a medical journal, and the FDA has not yet evaluated that claim, does not mean the statement is inherently misleading.⁷⁶ The FDA also admitted that if information about off-label uses originates from a source other than the manufacturer, or is given by the manufacturer at the request of a physician, then the FDA has no objection.⁷⁷ To the court, this stance was inconsistent with a claim that such statements are

⁷⁰ *Friedman*, 13 F. Supp. 2d at 66.

⁷¹ *Id.*

⁷² *Id.*

⁷³ *Id.* at 67 (citing Defendants Memorandum of Points and Authorities at 32).

⁷⁴ *Id.* at 67 (citing Final Guidance on Industry-Supported Scientific and Educational Activities, 62 Fed. Reg. 64074, 64079 (Dec. 3, 1997) (notice)).

⁷⁵ *Id.*

⁷⁶ *Id.* at 67.

⁷⁷ *Id.* at 67–68 (citing Hubbard Deposition at 46; Tart Deposition at 155).

inherently misleading, because a statement cannot be inherently misleading if it becomes problematic only in certain situations, or only when certain parties distribute the information.⁷⁸

The court then moved on to examining whether the restrictions on this lawful/non-misleading speech advanced any substantial government interests. The FDA claimed two such interests were promoted by their guidance documents: ensuring physicians receive accurate information about drugs, in order to make appropriate prescription decisions, and creating incentives for drug manufacturers to seek FDA approval for current off-label uses.⁷⁹ The court rejected the first rationale, refusing to recognize a paternalistic attempt to “protect” doctors from commercial speech as an important goal.⁸⁰ However, the FDA’s second submitted interest was sufficiently substantial to meet the second prong of the *Central Hudson* test. WLF tried to argue that moving a use from off-label to on-label does not necessarily promote greater public health.⁸¹ The court, on the other hand, pointed to the congressional requirement that all marketed uses for drugs be proven safe and effective by the FDA, and deferred to this determination of the importance of moving common uses for drugs onto the labeling.⁸²

Under the third prong of *Central Hudson*, the government restrictions must advance the substantial interest directly, providing more than “remote support.”⁸³ The court concluded the FDA’s regulations did directly advance the government’s interest in having off-label uses go through the approval process. Given the many economic incentives drug manufacturers have to

⁷⁸ *Id.* at 68.

⁷⁹ *Id.* at 69.

⁸⁰ *Id.* at 69–70. The court also explained that their rejection of this purported government interest fit with the Supreme Court’s historical refusal to “equate less information with better decision-making.” *Id.* at 70.

⁸¹ *Id.* at 71.

⁸² *Id.*

⁸³ *Central Hudson Gas & Elec. Corp. v. Public Service Commission of New York*, 447 U.S. 557, 564 (1980).

shirk the rigors of a supplemental NDA, the court was persuaded that the restrictions provide an appropriate counterbalance.⁸⁴

The fourth prong was the downfall for the FDA; the court found that the restrictions were far more expansive than was necessary for the government to achieve its goals.⁸⁵ While the court reiterated that the FDA was not required to adopt the least restrictive means available, the court explained they reached their decision largely because multiple other, less burdensome options existed.⁸⁶ As an acceptable alternative means, the court pointed to a more limited requirement that manufacturers simply be required to clearly disclose on the label that certain uses are not approved by the FDA.⁸⁷ Such a restriction, while clearly less inhibiting than the FDA's prior policies, would still achieve the FDA's goals, because there would be no danger in the speech being misleading and the incentive to get a supplemental NDA (and thus access to a wider variety of marketing opportunities) would still be present.⁸⁸ Because of this flaw, the court declared the policies, rules, and regulations contained in the FDA's guidance documents to be unconstitutional, and issued an injunction barring any U.S. agency from prohibiting drug and device manufacturers from distributing peer-reviewed journal articles or reference texts that discussed off-label uses.⁸⁹ Drug and device companies were also to be allowed to recommend speakers and topics to independent organizers of CME events, regardless of whether their recommendations would lead to off-label uses being discussed.⁹⁰

The district court's opinion in *Friedman* was handed down on July 30, 1998; on November 21, 1998, the FDAMA, through its implementing regulations, superseded the FDA's

⁸⁴ *Friedman*, 13 F. Supp. 2d at 72.

⁸⁵ *Id.* at 73.

⁸⁶ *Id.* at 73.

⁸⁷ *Id.* at 73.

⁸⁸ *Id.*

⁸⁹ *Id.* at 74.

⁹⁰ *Id.* at 74–75.

guidance documents regarding scientific journals and reference texts.⁹¹ WLF returned to the district court, claiming that the provisions of the FDAMA dealing with off-label use were inconsistent with the court's injunction.⁹² According to WLF, the FDAMA suffered the same constitutional defects as the FDA guidance because it severely restricted, in ways more restrictive than necessary, distribution of journal articles and reference texts regarding off-label uses.⁹³ In early 1999, the FDA asked that the injunction be modified to explicitly apply only to their 1996 and 1997 guidance documents, thus allowing the FDAMA's off-label promotion clauses to stand.⁹⁴ The court denied this request, and instead asked for supplemental briefs from both parties discussing the impact of the injunction on the FDAMA.⁹⁵ Later that year, the court determined that the FDAMA maintained the same policies held unconstitutional in *Friedman*, and therefore the FDA was enjoined from enforcing it.⁹⁶ The court acknowledged that the FDAMA modified the FDA's policy toward manufacturer distribution of articles and texts that discuss off-label uses, but it did not change the agency's approach so as to erase the unconstitutional nature of the restrictions.⁹⁷

After analyzing the parties' briefs, the court began by again applying the *Central Hudson* test for restrictions on commercial speech.⁹⁸ The court largely reiterated its analysis from *Friedman* regarding prongs one and two.⁹⁹ With respect to prong three, the court found that only one of the FDAMA's requirements directly advanced the government's legitimate interest in

⁹¹ Washington Legal Foundation v. Henney, 56 F. Supp. 2d 81, 83 (D.D.C. 1999). Because the FDAMA did not cover CME and other educational programming that drug and device manufacturers may become involved in, the FDA's guidance on the subject (62 Fed. Reg. 64074 (1997)) remained effective. Washington Legal Foundation v. Henney, 202 F.3d 331, 335 (D.C.Cir. 2000).

⁹² *Henney*, 56 F. Supp. 2d at 83.

⁹³ *Id.* at 83.

⁹⁴ Washington Legal Foundation v. Friedman, 36 F.Supp.2d 16, 18 (D.D.C. 1999).

⁹⁵ *Id.*

⁹⁶ *Henney*, 56 F. Supp. 2d at 84.

⁹⁷ *Id.* at 84.

⁹⁸ *Id.*

⁹⁹ *Id.* at 85–87.

incentivizing supplemental NDAs.¹⁰⁰ This provision granted manufacturers permission to distribute articles concerning off-label uses if they met one of three requirements: they submitted a supplemental NDA, certified to the FDA that they would soon be submitting a supplemental NDA, or the Secretary of Health and Human Services determined the manufacturer to be exempt from submitting a supplemental NDA (for example, because the associated clinical studies of the off-label use would be unethical or prohibitively expensive).¹⁰¹ The FDAMA's other restrictions on distribution, such as requiring an attached bibliography on all articles and reference texts discussing off-label uses, did advance the asserted goal of ensuring that physicians receive accurate and complete information, but this government interest was not a legitimate one under prong two.¹⁰²

However, the FDAMA provision that did directly advance a government interest failed prong four of *Central Hudson* because the means of achieving this goal were far more broad than necessary.¹⁰³ The court blasted the FDAMA for committing a kind of “constitutional blackmail,” by conditioning the exercise of First Amendment rights upon the submission of a supplemental NDA.¹⁰⁴ The 1998 injunction was then amended to explicitly declare the FDAMA and its implementing regulations unconstitutional.¹⁰⁵ The injunction made clear, however, that the FDA was still free to place limitations on the dissemination of false or misleading information, or to require certain disclosures regarding the unapproved nature of the uses discussed.¹⁰⁶

¹⁰⁰ *Id.* at 86–87.

¹⁰¹ *Id.*

¹⁰² *Id.* at 86.

¹⁰³ *Id.* at 87.

¹⁰⁴ *Id.*

¹⁰⁵ *Id.*

¹⁰⁶ *Id.* at 88.

The FDA appealed the district court’s decision,¹⁰⁷ but the anticipated constitutional battle never arose. During oral arguments before the D.C. Court of Appeals, the FDA made a strategic change in position, claiming that the FDAMA and 1997 guidance regarding educational activities (CME guidance) merely created “safe harbors”: if manufacturers meet these provisions, they would be safe from prosecution on the basis of the information they distributed or educational activity they were involved in.¹⁰⁸ However, in and of themselves these policies and regulations did not authorize the FDA to proscribe speech or grant the agency any independent prosecutorial authority.¹⁰⁹ If, for example, a pharmaceutical company violated the safe harbor provisions by distributing information without promising to file a supplemental NDA, then the FDA could still exercise its long-established authority to prosecute for misbranding.¹¹⁰

In response to the FDA’s new position, WLF no longer contended that the agency was unconstitutionally restricting commercial speech.¹¹¹ However, WLF, citing the principle that “voluntary cessation of challenged conduct will only moot a case if ‘subsequent events made it absolutely clear that the allegedly wrongful behavior could not reasonably be expected to recur,’” still asked the Court of Appeals to affirm the district court’s modification of the injunction.¹¹² If the court did not, the organization feared that the FDA would nonetheless subsequently prosecute violations of the FDAMA or CME guidance.¹¹³ The Court of Appeals refused to do so, explaining that the issue before the court was the facial constitutionality of the FDAMA and CME guidance, and because WLF agreed these policies were no longer unconstitutional under the FDA’s new interpretation, there was no longer a disagreement

¹⁰⁷ *Washington Legal Foundation v. Henney*, 202 F.3d 331 (D.C.Cir. 2000).

¹⁰⁸ *Id.* at 335–36.

¹⁰⁹ *Id.*

¹¹⁰ *Washington Legal Foundation v. Henney*, 128 F.Supp.2d 11, 13 (D.D.C. 2000).

¹¹¹ *Henney*, 202 F.3d at 336.

¹¹² *Id.* at 336.

¹¹³ *Id.* (quoting *United States v. Concentrated Phosphate Export Ass’n*, 393 U.S. 199, 203 (1968)).

between the parties.¹¹⁴ Furthermore, there was no issue of “voluntary cessation,” as WLF had made no claim of action taken by the FDA pursuant to the documents at issue.¹¹⁵ The Court of Appeals then vacated the lower court’s order and injunction to the extent they pronounced the FDAMA and CME guidance unconstitutional.¹¹⁶

In response to the Court of Appeals decision, the FDA in March 2000 issued a notice explaining the scope of their regulatory power.¹¹⁷ The FDA reiterated that if drug and device manufacturers fail to follow the FDAMA or CME guidance, this is not an independent violation of the law.¹¹⁸ However if a manufacturer does not comply with the safe harbors established therein, the FDA “may bring an enforcement action under the FDCA, and seek to use journal articles and reference texts disseminated by the manufacturer as evidence that an approved product is intended for a ‘new use.’”¹¹⁹ In the final court case of the saga, WLF responded to this notice by returning to the district court.¹²⁰ WLF complained that, by using dissemination of journal articles as evidence of a new, off-label use, and then prosecuting for misbranding, the FDA was effectuating the same policies which the district court had declared unconstitutional in 1999.¹²¹ In a terse response, the district court explained that, because the Court of Appeals “wholly vacated” their injunction, there was nothing the FDA’s notice could violate.¹²² The district court criticized the FDA for completely obfuscating any sense of permissible conduct for pharmaceutical companies in this area, and expressed frustration with the Court of Appeals for

¹¹⁴ *Id.*

¹¹⁵ *Id.*

¹¹⁶ *Id.* at 337.

¹¹⁷ Decision in *Washington Legal Foundation v. Henney*, 65 Fed. Reg. 14286 (March 16, 2000) (notice).

¹¹⁸ *Id.* at 14287.

¹¹⁹ *Id.*

¹²⁰ *Washington Legal Foundation v. Henney*, 128 F.Supp.2d 11 (D.D.C. 2000).

¹²¹ *Id.* at 13.

¹²² *Id.* at 15.

dodging the issue, instead of using the opportunity to provide finality and clarity.¹²³ The court ended the Washington Legal Foundation series of cases with a prediction: given the lack of definitive answers generated by the litigation, they would soon be required to weigh in on the issue again.¹²⁴

IV. Recent Constitutional Challenges

Recently, the FDA has stepped up their prosecution of off-label promotion. Such cases virtually always end in settlement because pharmaceutical companies are risk-averse: they fear potentially higher penalties that could be meted down after a court conviction, as well as possible agency retaliation if they fight back and contest the charges.¹²⁵ Additionally, off-label promotion can sometimes be attached to a larger charge of defrauding the government, conviction of which leads to a mandatory five-year exclusion from the profitable Medicare and Medicaid programs.¹²⁶ In the past twenty years, there have been 165 settlements between the FDA and the pharmaceutical industry, with a total of \$19.8 billion paid out in penalties.¹²⁷ 121 of the

¹²³ *Id.*

¹²⁴ *Id.*

¹²⁵ Post of Jim Beck & Mark Herrmann to Drug and Device Law, <http://druganddevicelaw.blogspot.com/2009/10/off-label-use-times-they-are-changin.html> (Oct. 8, 2009, 14:24 EST).

¹²⁶ *Testimony on Medical Exclusions: Hearing Before the Subcomm. on Human Resources and Intergovernmental Affairs of the H. Comm. on Government Reform and Oversight*, 105th Cong. (1997) (statement of June Gibbs Brown, Inspector Gen., U.S. Dep't of Health and Human Servs.), *available at* <http://www.hhs.gov/asl/testify/t960905a.html> (citing Health Insurance Portability and Accountability Act of 1996, PL 104-191)). However, some drug manufacturers have been deemed too essential to be excluded from Medicare/Medicaid, because consumers participating in these government health insurance programs would suffer too much if the products were not available to them. Under the government's permitting eyes, pharmaceutical companies that are "too big to fail" can create a subsidiary shell company, which the government then excludes from Medicare/Medicaid, while the parent company is still allowed to participate and sell its products. *See, e.g.,* Drew Griffin & Andy Segal, *Feds Found Pfizer Too Big to Fail*, CNN, Apr. 2, 2010, <http://www.cnn.com/2010/HEALTH/04/02/pfizer.bextra/index.html?hpt=T2>.

¹²⁷ ALMASHAT ET AL., *supra* note 1, at 2.

settlements, constituting \$14.8 billion in penalties, have occurred in the past five years.¹²⁸ Some commentators explain that this phenomenon of increasing penalties is the result of pharmaceutical companies pursuing increasingly aggressive promotional practices in the face of temptingly lucrative profits from off-label drug sales.¹²⁹ Despite large fines, the profits from increased off-label prescribing can more than make up the difference. When Pfizer was prosecuted for promotional practices surrounding its Cox-2 inhibitor Bextra, for example, the \$1.2 billion fine ultimately levied represented only three months' profit for the company.¹³⁰

These heightened penalties have led to renewed claims that the FDA's policies unconstitutionally infringe on the First Amendment protections of commercial speech. This time, however, the issue is being raised not by third party advocacy groups, but rather by the parties being investigated for off-label promotion. One of the most high-profile instances occurred in the fall of 2009 when Allergan, the maker of Botox, decided to fight back after the FDA filed charges alleging that the company was aggressively promoting Botox for multiple off-label uses.¹³¹

Botox is approved to treat several conditions, such as crossed eyes and involuntary neck contractions.¹³² Physicians frequently prescribe Botox for patients who are dealing with conditions associated with spasticity, such as the involuntary muscle contractions suffered by those with cerebral palsy.¹³³ While treating spasticity is not an FDA-approved use for Botox,¹³⁴ the drug has become so frequently prescribed in this area that the United States Pharmacopeia

¹²⁸ *Id.*

¹²⁹ See, e.g., David Evans, *When Drug Makers' Profits Outweigh Penalties*, WASH. POST, Mar. 21, 2010, at G1.

¹³⁰ See, e.g., Griffin & Segal, *supra* note 121.

¹³¹ Press Release, Dep't of Justice, Office of Pub. Affairs, Allergan Agrees to Plead Guilty and Pay \$600 Million to Resolve Allegations of Off-Label Promotion of Botox (Sept. 1, 2010), *available at* <http://www.justice.gov/opa/pr/2010/September/10-civ-988.html>.

¹³² Complaint ¶ 51, Allergan, Inc. v. United States, No. 09-1879 (D.D.C. Oct. 1, 2009).

¹³³ *Id.* ¶¶ 55–56.

¹³⁴ *Id.* ¶ 56.

and Drugdex compendiums have listed the product every year since 2002 for at least one spasticity-related indication,¹³⁵ and Botox prescriptions written to treat spasticity are reimbursed by Medicare.¹³⁶ Allergan was also working to move this use on-label, and had submitted a supplemental Biologics License Application in August 2008, requesting FDA approval for using Botox to treat upper-limb spasticity after stroke.¹³⁷

The FDA, through its Adverse Event Reporting System, had received information about adverse side effects in Botox users, both for approved and unapproved uses.¹³⁸ In response, the FDA asked Allergan to update the labeling on Botox.¹³⁹ Allergan's proposed labeling was rejected by the FDA, and the company ultimately implemented the FDA-suggested version.¹⁴⁰ This label singled out an elevated risk of respiratory complications in children receiving Botox to treat spasticity.¹⁴¹ Allergan wanted to supplement this new labeling with additional, more detailed information for physicians regarding Botox and spasticity treatment, such as optimal injection sites and dosage levels, in order to reduce the risk of adverse events.¹⁴² The proposed distribution of information would have been in the form of print and electronic communications to physicians, as well as presentations at the meetings of professional societies.¹⁴³ The information would not have modified any of the current labeling on the product itself.¹⁴⁴ Allergan explains that the current regulatory regime puts them at risk for criminal charges and financial penalties if they disseminate this truthful, non-misleading information to physicians

¹³⁵ *Id.* ¶ 61.

¹³⁶ *Id.* ¶ 63. A recent district court case actually held that Congress intended for medically beneficial off-label uses to be covered by Medicare. *Layzer v. Leavitt*, 2011 WL 813822, at *5 (S.D.N.Y. Mar. 7, 2011).

¹³⁷ Complaint, *supra* note 127, ¶ 57.

¹³⁸ *Id.* ¶¶ 65–66.

¹³⁹ *Id.* ¶ 66.

¹⁴⁰ *Id.* ¶¶ 67–73.

¹⁴¹ *Id.* ¶¶ 67–72.

¹⁴² *Id.* ¶¶ 76–77.

¹⁴³ *Id.* ¶¶ 85–87.

¹⁴⁴ *Id.* ¶¶ 88–89.

about how to minimize the risks associated with the current off-label uses of their products. Claiming that such restrictions on truthful speech are unconstitutional, in October of 2009 Allergan sued the FDA in the District Court for the District of Columbia, for infringing upon their First Amendment rights.¹⁴⁵ On the same day, Allergan also filed a motion seeking a preliminary injunction, in order to prevent the FDA from using the FD&C Act and agency regulations to chill their proposed speech.¹⁴⁶ Although Allergan ultimately dropped their suit as part of a settlement deal in October 2010,¹⁴⁷ their complaint, in conjunction with the documents the government submitted in response,¹⁴⁸ create a fairly well-developed view of the issues at the heart of this debate.

Allergan claimed that the regulatory regime is facially unconstitutional in four main aspects.¹⁴⁹ Count I of the complaint alleged that the definition of “labeling,” as promulgated by the FDA in 21 C.F.R. § 202.1(l)(2), is unconstitutional. The FD&C Act defines “labeling” as “all labels and other written, printed, or graphic material (1) upon any article or any of its containers or wrappers, or (2) accompanying such article.”¹⁵⁰ Allergan argued the FDA redefined “labeling” in a way that “extend[s] far beyond its statutory mooring,” and the agency will not be able to prove that this unrestrained new definition of “labeling” is no more restrictive than necessary, as required by prong four of the *Central Hudson* test for acceptable limitations on

¹⁴⁵ *Id.* ¶¶ 88, 94.

¹⁴⁶ Plaintiff’s Memorandum of Law in Support of Motion for Preliminary Injunction, Allergan, Inc. v. United States, No. 09-1879 (D.D.C. Oct. 1, 2009) [hereinafter Plaintiff’s Motion for Preliminary Injunction].

¹⁴⁷ Dep’t of Justice, Office of Pub. Affairs, *supra* note 126.

¹⁴⁸ Defendants’ Memorandum of Points and Authorities in Support of Motion to Dismiss or For Summary Judgment, Allergan, Inc. v. United States, No. 09-1879 (D.D.C. Jan. 11, 2010) [hereinafter Defendants’ Motion to Dismiss].

¹⁴⁹ Allergan made several as-applied constitutional arguments as well; for the scope of this paper, I will be focusing on their facial challenges.

¹⁵⁰ 21 U.S.C. § 321(m) (2009).

commercial speech.¹⁵¹ To support their contention, Allergan pointed to the expansive list of materials the FDA stated they would consider to be labeling. This list includes:

Brochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, sound recordings, exhibits, literature, and reprints and similar pieces of printed, audio, or visual matter descriptive of a drug and references published (for example, the “Physicians Desk Reference”) for use by medical practitioners, pharmacists, or nurses, containing drug information supplied by the manufacturer, packer, or distributor of the drug and which are disseminated by or on behalf of its manufacturer, packer, or distributor are hereby determined to be labeling as defined in section 201(m) of the act.¹⁵²

From Allergan’s perspective, this regulation turns any tangible material distributed by a manufacturer and containing manufacturer-provided drug information into “labeling.”¹⁵³ As a result, a conflict is formed between the FD&C Act, which creates FDA jurisdiction over materials on or “accompany[ing]” the drug, and the agency-promulgated regulation, which drops the “accompany” requirement of 21 U.S.C. § 321(m).¹⁵⁴ The defendants maintained that the definition in 21 C.F.R. § 202.1(l)(2) falls within their statutory authority as interpreted by the Supreme Court over sixty years ago in *United States v. Kordel*.¹⁵⁵ *Kordel* defines “accompany” broadly, as any material that “supplements or explains” the product.¹⁵⁶ The focus is on the functional and textual relationship between a drug and the material alleged to be “labeling.”¹⁵⁷ The government maintained that the materials listed in 21 C.F.R. § 202.1(l)(2) are all items that “accompany” drugs in a functional, *Kordel* sense of the word; thus the regulation preserves, albeit implicitly, the requirement that labeling “accompany” the regulated product.¹⁵⁸

¹⁵¹ Plaintiff’s Motion for Preliminary Injunction, *supra* note 141, at 33–35.

¹⁵² 21 C.F.R. § 202.1(l)(2) (2008).

¹⁵³ Plaintiff’s Motion for Preliminary Injunction, *supra* note 141, at 33.

¹⁵⁴ *Id.* at 32–33.

¹⁵⁵ *Id.* at 32 (citing *United States v. Kordel*, 335 U.S. 345, 348–50 (1948)).

¹⁵⁶ *Kordel*, 335 U.S. at 350.

¹⁵⁷ See Defendants’ Motion to Dismiss, *supra* note 143, at 32–33.

¹⁵⁸ See Defendants’ Motion to Dismiss, *supra* note 143, at 34–35.

In contrast, Allergen interpreted “accompany” to mean materials “sent along with . . . [the product] in connection with its sale” and “distributed along with the drug.”¹⁵⁹ Allergan cited dictionary definitions and focused on the “ordinary meaning” of “accompany” to argue that Congress did not intend the word to be so broad as to include materials not sent with a drug in connection with its sale.¹⁶⁰ Allergen did not disavow the *Kordel* definition of “accompany,” and in fact cited the case in support of their motion for preliminary injunction.¹⁶¹ However, Allergan criticized the government for selectively relying on certain phrases in *Kordel*.¹⁶² Per Allergan’s interpretation, *Kordel* put forth a more limited holding than that cited by the government, essentially creating a four-factor test: written materials will be deemed to accompany a product, despite being sent in a different shipment, if they are “(1) sent from the same place; (2) to the same place; (3) as part of an ‘integrated . . . transactio[n]’; and (4) they ‘supplement or explain’ the use of the drug, thereby having a ‘textual relationship’ to it.”¹⁶³

This seems to be a stretched reading of *Kordel*. The Court makes a sweeping statement that “one article or thing is accompanied by another when it supplements or explains it,” and nowhere in the opinion does the Court indicate this is limited to situations involving products sent to and from the same location. The Court did emphasize that the transactions involved were too “integrated” to allow the defendants to claim that the explanatory materials sent in another

¹⁵⁹ See Plaintiff’s Motion for Preliminary Injunction, *supra* note 141, at 33, 35–36.

¹⁶⁰ *Id.* at 35–36.

¹⁶¹ *Id.* at 33.

¹⁶² *Id.* at 37.

¹⁶³ *Id.* (citing *United States v. Kordel*, 335 U.S. 345, 348–50 (1948)). Note that in their Motion to Dismiss, the government mistakenly describes this test as indicative of Allergan’s definition of “accompany.” See Defendants’ Motion to Dismiss, *supra* note 143, at 32. This is inaccurate because Allergan did not offer this test as the definition of “accompany,” but instead used this interpretation to rebut the government’s insistence that *Kordel* created a broad definition of “accompany.” Per Allergan’s interpretation, the Court described a narrow set of circumstances that, when fulfilled, would be sufficient to deem materials physically separate from drugs to be labeling. Allergan made no claim that these conditions are necessary in that materials and drugs “accompany” each other *only if* going to and from the same place. Allergan does seem to provide a definition of “accompany,” however: materials sent in connection with the drug’s future sale, and which are distributed together. See Plaintiff’s Motion for Preliminary Injunction, *supra* note 141, at 33, 35.

package did not constitute “labeling.” However, the Court’s discussion in this regard did not connote the physical restrictions Allergan seeks to read into the opinion. Instead, the explanation functioned mainly to support the Court’s point that if written materials and a product are so connected that one explains the other, this integration is sufficient to create a nexus such that the material will still be deemed labeling, despite geographical or temporal distance. Because of the broad holding in *Kordel*, Allergan probably would have lost the claim that 21 C.F.R. § 201.1(l)(2) directly conflicts with 21 U.S.C. § 321(m).

Perhaps recognizing the weakness of their *Kordel* interpretation, Allergan retreated fairly quickly to an alternate argument, claiming that the district court should apply the canon of constitutional avoidance: In order to circumvent possible First Amendment concerns about the breadth of the FDA’s ability to restrict speech, the court should interpret the word “accompany” narrowly, so as not to include materials generally distributed to physicians and unconnected with the sale of products.¹⁶⁴ Allergan cited the D.C. Circuit’s 2008 decision in *Kemphorne* for the proposition that “the canon of constitutional avoidance trumps *Chevron* deference.”¹⁶⁵ Although the *Kemphorne* court ultimately found the constitutional issues raised by the plaintiffs to be insufficiently “serious” to warrant abandoning *Chevron* deference,¹⁶⁶ five years earlier the court did refuse to accord such deference to a government agency that “failed to tailor its disclosure policy to avoid unnecessarily infringing upon [the plaintiff’s] First Amendment rights.”¹⁶⁷ The government’s court filings never addressed the canon of constitutional avoidance, but they may have had reason to worry. Particularly in situations where a pharmaceutical company had

¹⁶⁴ Plaintiff’s Motion for Preliminary Injunction, *supra* note 141, at 37.

¹⁶⁵ Plaintiff’s Memorandum of Law in Support of Cross-Motion for Summary Judgment and In Opposition to Motion to Dismiss or for Summary Judgment at 33–34, *Allergan, Inc. v. United States*, No. 09-1879 (D.D.C. Jan. 15, 2010) [hereinafter Plaintiff’s Cross-Motion for Summary Judgment] (citing *Nat’l Mining Ass’n v. Kemphorne*, 512 F.3d 702, 711 (D.C. Cir. 2008)).

¹⁶⁶ *Kemphorne*, 512 F.3d at 711.

¹⁶⁷ *AFL-CIO v. FEC*, 333 F.3d 168, 175 (D.C. Cir. 2003).

already applied for a supplemental NDA, the court may well have found the speech restrictions sufficiently serious to warrant a refusal to apply *Chevron* deference to the FDA interpretation of “accompany.”

In Count II of their complaint, Allergan claimed that 21 U.S.C. § 352(a), which renders misbranded any drug with labeling that is “false or misleading in any particular,” is unconstitutional when used to restrict truthful, non-misleading statements.¹⁶⁸ Allergan explained that under the government’s interpretation of the FD&C Act, § 352(a) operates to ban all “labeling” mentioning off-label uses if the FDA has not reviewed and approved the statement.¹⁶⁹ This ban is implemented regardless of whether the statements are truthful and accurately depict scientific research.¹⁷⁰ As a result, the government is essentially banning truthful speech because it has not been approved by the government, the very essence of a First Amendment violation.¹⁷¹

To support this allegation about FDA policy, Allergan pointed to the government’s prior statements during the 2004 prosecution of Warner-Lambert for off-label promotion. In the sentencing memorandum, the government stated that pharmaceutical companies would violate § 352(a) simply by making a “suggest[ion] that a drug is safe and effective for uses which have not been approved by the FDA.”¹⁷² In its Motion to Dismiss, the government admitted they made this statement, but explained that Allergan had taken the remark out of context. Warner-Lambert had made promotional claims regarding the safety and effectiveness of one of their products, despite an earlier rejection by the FDA for such a use. In the context of a prior FDA rejection, then, it is false and misleading for a pharmaceutical company to “suggest that a drug is safe and

¹⁶⁸ Complaint, *supra* note 127, ¶¶ 112–13.

¹⁶⁹ Plaintiff’s Motion for Preliminary Injunction, *supra* note 141, at 38.

¹⁷⁰ *Id.*

¹⁷¹ *Id.*; Complaint, *supra* note 127, ¶¶ 112–16.

¹⁷² Complaint, *supra* note 127, ¶ 29 (quoting U.S. Sentencing Memo., United States v. Warner-Lambert Co., No. 04-10150, at 8–9 (D. Mass. 2004)).

effective for uses which have not been approved by the FDA,” a more narrow proposition the government continued to defend as legitimately within their regulatory purview.¹⁷³

The government maintained that, absent such a prior FDA rejection, statements by manufacturers regarding the safety and effectiveness of unapproved uses are not inherently misleading, simply because the FDA has not granted its imprimatur to the claims.¹⁷⁴ To prove this was the Agency’s position, the government pointed to 21 C.F.R. § 201.56(a)(3), a regulation which prohibits the labeling on prescription drugs from including implied claims or suggestions if these claims rest on “inadequate evidence of safety or a lack of substantial evidence of effectiveness.”¹⁷⁵ If the FDA’s position was truly as Allergan claimed, they responded, then 21 C.F.R. § 201.56(a)(3) would be completely redundant, because even if an implied claim was accompanied by adequate proof of safety and effectiveness, it would still be inherently misleading without FDA approval, and thus prohibited.¹⁷⁶ For further support, the government pointed to analogous statements made to the court by Dr. Robert Temple, Director of the Office of Medical Policy in the FDA’s Center for Drug Evaluation and Research.¹⁷⁷

It is significant that while contesting Allergan’s claim, the government could point to no agency statement or action in order to affirmatively show that the reigning policy was other than as Allergan described. Instead, they were relegated to indirectly proving that this could not be their policy because it conflicted with the implications of other regulations. Furthermore, if a producer’s statement about his product’s safety and efficacy for an unapproved use is not inherently “false or misleading,” simply because it lacks FDA approval, then the question

¹⁷³ Defendants’ Motion to Dismiss, *supra* note 143, at 35 n. 12 (citing United States v. Warner-Lambert Co., No. 04-10150, at 8–9 (D. Mass. 2004)).

¹⁷⁴ *Id.* at 34–35.

¹⁷⁵ *Id.* at 34 n. 11 (quoting 21 C.F.R. § 201.56(a)(3) (2006)).

¹⁷⁶ *Id.*

¹⁷⁷ *Id.*; FOOD AND DRUG ADMINISTRATION, MAKING SENSE OF VYTORIN CONCERNS 1 (2008), available at <http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/ucm048510.pdf>.

remains: what determines the line between off-label claims for unapproved uses that are false and misleading, and those that are not? The government did not illuminate the distinction, declaring only that references to unapproved uses as part of labeling “*can* be false or misleading.”¹⁷⁸

In an attempt to provide some clarity, the government gave two examples of speech regarding off-label uses that will be held to be “false and misleading” under § 352(a): if a drug company implies that the FDA approved the drug, when in fact the agency did not, and when a drug company implies that a product’s safety and effectiveness have been proven, when they have not. But by using two examples of blatantly and objectively false statements, the government inappropriately shifts the scope of the argument. The heart of the issue is an inquiry into when, if at all, *truthful* statements about off-label uses can be struck down as “false and misleading.” While the government may have successfully proven that they never established a policy branding such statements as always “false and misleading,” the inquiry remains: when does the government label such truthful claims as “false and misleading”? When is it constitutionally acceptable to do so?

The lack of clarity for drug and device manufacturers is problematic. As of now, the only way manufacturers can receive a hint of the rules that will be applied to them is through FDA-issued guidance. For example, the January 2009 guidance¹⁷⁹ helped establish a line between truthful journal reprints that will and will not be interpreted as claiming a new use for the drug (if the latter, the drug would be rendered misbranded, because the labeling does not discuss all of

¹⁷⁸ Defendants’ Motion to Dismiss, *supra* note 143, at 35.

¹⁷⁹ Guidance for Industry on Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices, 74 Fed. Reg. 1694-01 (Jan. 13, 2009) (notice).

the drug's uses). However, because the January 2009 guidance is limited to the relatively narrow scope of journal articles, it is only a small step toward fixing a much larger problem.

Count III of Allergan's complaint entailed a claim that 21 C.F.R. § 202.1(e)(4)(i)(a), which bans advertisements of off-label uses, is unconstitutional, or invalid as an unreasonable interpretation of § 352(n) of the FD&C Act.¹⁸⁰ § 352(n) of the FD&C Act renders advertisements for prescription drugs "misbranded," and thus barred from interstate commerce, if they fail to disclose the "established name" of the drug, its chemical formula, and a summary of other "information . . . relating to its side effects, contraindications, and effectiveness" as the Secretary of Health and Human Services may choose to require.¹⁸¹ If these hurdles are met, then the prescription drug advertisement is legal under the FD&C Act.¹⁸² The FDA promulgated 21 C.F.R. § 202.1 to further detail the requirements for prescription drug advertisements.¹⁸³ Allergan claimed subsection (e)(4)(i)(a) of this regulation is in conflict with § 352(n), because the former creates an additional requirement not found in the FD&C Act: a drug is "misbranded" if any advertisement for the product "recommend[s] or suggest[s]" an off-label use, regardless of whether the drug's advertisements meet all of the disclosure requirements set forth in § 352(n).¹⁸⁴ This added condition renders subsection (e)(4)(i)(a) invalid as an unreasonable interpretation of § 352(n).¹⁸⁵ Additionally, Allergan maintained that, by creating a per se ban on off-label prescription drug advertising, subsection (e)(4)(i)(a) is unconstitutional because its restriction on free speech is far broader than necessary to achieve the government's goal of

¹⁸⁰ Complaint, *supra* note 127, ¶¶ 120–22.

¹⁸¹ *Id.* ¶ 119 (citing 21 U.S.C. § 352(n) (2007)).

¹⁸² Plaintiff's Motion for Preliminary Injunction, *supra* note 141, at 41.

¹⁸³ Defendants' Motion to Dismiss, *supra* note 143, at 24.

¹⁸⁴ Complaint, *supra* note 127, ¶ 120 (citing 21 C.F.R. § 202.1(e)(4)(i)(a)).

¹⁸⁵ *Id.* ¶ 122.

incentivizing FDA approval for off-label uses.¹⁸⁶ As an example of less restrictive policies the government could implement, Allergan cited an alternate rule that would require manufacturers to simply disclose in the advertisement that the off-label use is not FDA approved.¹⁸⁷ However, prohibiting all off-label advertisements, without distinguishing between ones that are truthful and non-misleading and ones that are not, or ones that meet the disclosure requirements of § 352(n) and ones that do not, is far too broad to be sustained under *Central Hudson*.¹⁸⁸

The government responded by first explaining how 21 C.F.R. § 202.1(e)(4)(i)(a) is consistent with § 352(n). § 352(n) allows the Secretary to require advertisements to contain certain “information . . . relating to . . . effectiveness,” which necessarily includes information about the product’s effectiveness in the field of unapproved uses.¹⁸⁹ The FDA can choose, as it has, to limit advertisements’ information about effectiveness to claims that have been proven through the new drug approval process.¹⁹⁰

The government also crafted an argument for why 21 C.F.R. § 202.1(e)(4)(i)(a) does not conflict with the First Amendment under *Central Hudson*’s analysis. The government first claimed that because this regulation deals with speech that promotes an illegal activity, it does not receive First Amendment protection. During the 1998 Washington Legal Foundation case, the District Court of the District of Columbia, as discussed above, defined the critical inquiry under *Central Hudson* prong number one as being whether the commercial speech encourages a lawful activity, and not, as the government suggested, whether the speech itself violates a law or regulation.¹⁹¹ Tailoring their argument to that earlier court’s language, the government sought to

¹⁸⁶ Plaintiff’s Motion for Preliminary Injunction, *supra* note 141, at 40–41.

¹⁸⁷ *Id.* at 40.

¹⁸⁸ *Id.* at 41.

¹⁸⁹ Defendants’ Motion to Dismiss, *supra* note 143, at 24–25.

¹⁹⁰ *Id.* at 25.

¹⁹¹ *Washington Legal Foundation v. Friedman*, 13 F. Supp. 2d 51, 66 (D.D.C. 1998).

frame the issue in terms of promoting an illegal activity. In the penultimate Washington Legal Foundation case, the Court of Appeals for the District of Columbia accepted the agency's interpretation of §§ 331(d), 355 of the FD&C Act, which rendered it illegal for a manufacturer to introduce a drug into interstate commerce if he intends that it be used for off-label purposes.¹⁹² Seizing upon this approval of their interpretation, the government argued in their Motion to Dismiss that advertisement of off-label uses does promote an unlawful activity: a manufacturer's introduction of drugs into the stream of commerce with the intent that they be sold for the off-label uses advertised.¹⁹³ Therefore, such speech should not receive First Amendment protection.¹⁹⁴ This argument fits the district court's prior analysis, and the best move likely would be to focus on the FDA's interpretation of § 352(n) as creating an overbroad restriction on speech.

The government relied heavily on public policy consequences in defending the Agency's interpretation. The pre-market system of drug approval created by Congress in 1962 was intended to minimize the sale of unsafe or ineffective drugs. The FDA's ban on prescription drug advertisements that recommend or suggest off-label uses directly furthers this goal, because it prevents manufacturers from obtaining FDA approval for a narrow swath of uses, and then marketing the drug for a variety of other, untested uses.¹⁹⁵ Even though 21 C.F.R. § 202.1(e)(4)(i)(a) bans both truthful and misleading advertisements without differentiation, the regulation is not overly broad under prong four of *Central Hudson* because the pre-1962 regime, which allowed all advertising claims and then prosecuted the makers of false and misleading ones after the fact, was recognized by the Supreme Court as "cumbersome," failing to meet the

¹⁹² Washington Legal Foundation v. Henney, 202 F.3d 331, 332–33 (D.C. Cir. 2000)

¹⁹³ Defendants' Motion to Dismiss, *supra* note 143, at 26 (citing *Henney*, 202 F.3d at 332 (D.C. Cir. 2000)).

¹⁹⁴ *Id.*

¹⁹⁵ *Id.* at 27.

regulatory needs of the public.¹⁹⁶ The government then went on to criticize the less restrictive suggestions Allergan had put forth as undermining the FD&C Act's goals.¹⁹⁷ By implication, the government argued that identifying other, less restrictive but overly permissive laws cannot lead to the conclusion that the current regime, which is broader but effective, is overly broad. The government ended their argument by assuring the court that § 202.1(e)(4)(i)(a) only seeks to prevent promotional speech about off-label uses, and would not prevent drug and device manufacturers from supplying non-promotional safety information to physicians.¹⁹⁸

The fourth and final facial challenge Allergan presented involved a claim that the FDA's "intended use" regulations were unconstitutional when used to restrict truthful, non-misleading speech about off-label uses.¹⁹⁹ In general, a drug is "misbranded" if its labeling does not contain "adequate directions for use."²⁰⁰ However, under § 353(b), prescription drugs are exempt from most of the FD&C Act's labeling requirements, including the adequate directions provision.²⁰¹ Instead, prescription drugs are misbranded only if their labeling does not exhibit the designator "Rx only."²⁰² Per their regulations, the FDA interpreted the statutory exemptions to apply only if prescription drugs have labeling indicating "adequate information for its use."²⁰³ Because the FD&C Act specifically exempts prescription drugs from the "adequate directions for use" requirement, among other misbranding provisions, Allergan contended that the FDA requirement of "adequate information for use" is in direct conflict with the FD&C Act.²⁰⁴

¹⁹⁶ *Id.* at 27–28.

¹⁹⁷ *Id.* at 28.

¹⁹⁸ *Id.* at 29.

¹⁹⁹ Complaint, *supra* note 127, ¶ 132.

²⁰⁰ *Id.* ¶ 127 (quoting 21 U.S.C. § 352(f)(1) (2007)).

²⁰¹ *Id.* ¶ 128 (quoting 21 U.S.C. §§ 353(b)(2), (4) (2004)).

²⁰² *Id.* (quoting §§ 353(b)(2), (4)).

²⁰³ Complaint, *supra* note 127, ¶ 129 (quoting 21 C.F.R. § 201.100(c)(1) (2006)); Defendants' Motion to Dismiss, *supra* note 143, at 29.

²⁰⁴ Complaint, *supra* note 127, ¶ 128–30.

The government responded that there was no conflict, because Allergan was misinterpreting the FD&C Act to create an overly broad total exemption for prescription drugs from the “adequate directions for use” requirement.²⁰⁵ Per the government’s interpretation, § 353(b) affords only a more limited exemption, occurring at the point where the prescription drug is “prescribed and dispensed” by a physician.²⁰⁶ Although the FD&C Act does not explicitly constrict the exception in this way, the FDA and the 5th Circuit have interpreted the exemption to take on these narrower contours based on the statutory language that the exemption applies to drugs that are “dispensed by filling or refilling” a prescription.²⁰⁷ In support of this reading, the FDA cites the canon of interpretation that exemptions are to be read narrowly.²⁰⁸ However, this is truly a very narrow reading of § 353(b). Particularly given the scant case law supporting the agency’s interpretation, Allergan seems to be on solid footing in challenging the reasonableness of the FDA’s statutory reading.

Allergan also contended that the FDA’s “intended use” regulations resulted in a “free-speech Catch 22.”²⁰⁹ 21 C.F.R. § 201.100 defines “adequate information” to be information sufficient to allow physicians to “use the drug safely and for the purposes *for which it is intended*” (emphasis added).²¹⁰ Under 21 C.F.R. § 201.128, the “intended use” for a product is broadly determined by examining the maker’s “objective intent,” which can be shown not simply by the product’s labeling, but through other oral or written statements.²¹¹ Additionally, FDA regulations impute an “intended use” upon a manufacturer who “knows, or has knowledge of

²⁰⁵ Defendants’ Motion to Dismiss, *supra* note 143, at 30.

²⁰⁶ *Id.* (quoting *United States v. Evers*, 643 F.3d 1043, 1051 (8th Cir. 1981)).

²⁰⁷ *Id.* (quoting 21 U.S.C. § 353(b)(2) (2004)).

²⁰⁸ *Id.*

²⁰⁹ Plaintiff’s Motion for Preliminary Injunction, *supra* note 141, at 26.

²¹⁰ Complaint, *supra* note 127, ¶ 131 (quoting 21 C.F.R. § 201.100(c)(1) (2006)).

²¹¹ Complaint, *supra* note 127, ¶ 132 (quoting 21 C.F.R. § 201.128) (1999)).

facts that would give him notice” about a use for the product.²¹² Thus, if a manufacturer is aware of off-label uses for his product, under FDA regulations this is an intended use. In order for “adequate information” to be present—allowing the drug to be exempt from certain labeling requirements—the manufacturer must place an explanation of this use on the label.²¹³ Yet under §§ 321(p) and 355(a), manufacturers are not allowed to discuss off-label uses as part of their product’s labeling.²¹⁴ Furthermore, Allergan claimed the FDA’s regulations prevent the very behavior they sought to induce.²¹⁵ In order to apply for a supplemental NDA, a company needs to not only have notice of an off-label use, they need compile data on the product’s safety and efficacy. Yet having this knowledge and gathering data about the off-label use indicates the manufacturer’s “objective intent” that their product be utilized off-label, leaving the manufacturer in violation of misbranding provisions.²¹⁶

The government responded by first explaining the well-established rule that speech may be used as evidence of intended use, even if regulatory or criminal penalties are thereby triggered.²¹⁷ Then, the government corrected what they termed Allergan’s “mischaracterization” of 21 C.F.R. § 201.128.²¹⁸ The regulation states a manufacturer’s intended use “may” be indicated by its “oral or written statements,” but does not state that every statement about an off-label use will inherently be treated as evidence of an intended use.²¹⁹ Citing only to the prior testimony of Dr. Temple, the government maintained it is the FDA’s position that certain statements about intended uses, namely non-promotional safety information, are not considered

²¹² *Id.* (quoting § 201.128)).

²¹³ *Id.*

²¹⁴ *Id.*

²¹⁵ Plaintiff’s Motion for Preliminary Injunction, *supra* note 141, at 26.

²¹⁶ *Id.* at 26–27.

²¹⁷ Defendants’ Motion to Dismiss, *supra* note 143, at 20 (citing *Wisconsin v. Mitchell*, 508 U.S. 476 (1993); *Whitaker v. Thompson*, 333 F.3d 947 (D.C. Cir. 2004)).

²¹⁸ *Id.*

²¹⁹ *Id.* at 21.

evidence of “intended use” within the regulatory meaning of the phrase.²²⁰ Similarly, FDA regulations did not require the Agency to treat a manufacturer’s knowledge of an intended use as objective intent to sell the product for an off-label use.²²¹ Instead, the FDA merely has the discretion to do so, and according to Dr. Temple, the agency “usually does not treat an unapproved use as an intended use solely because the manufacturer knows that the unapproved use is taking place.”²²² The government further asserted that the purported regulatory Catch-22 was purely a function of Allergan’s impatience to promote their product before FDA approval of the new use.²²³ This is because the FDA would not seek prosecution for misbranding based on a manufacturer waiting until their supplemental NDA was approved before changing the product’s labeling to add the formerly off-label uses.²²⁴ If a manufacturer was pursuing trials toward the goal of approval for the off-label use, the Agency claimed it similarly would not prosecute the producer for distributing the drug in its current labeling, as long as the maker did not promote the off-label use.²²⁵

The government’s responses here seem to constitute a weak defense. If the regulations grant the FDA permission to prosecute a manufacturer in such a situation, then a promise in a court brief that they will not exercise such authority does not answer a charge of constitutional defects. The crux of Allergan’s claim is that the FDA regulatory scheme chills their protected commercial speech. If the agency has broad discretion to prosecute drug and device manufacturers for their truthful speech, a defense that they don’t always exercise such authority is no defense at all. The truthful speech is still chilled, regardless of whether the FDA chooses to

²²⁰ *Id.*

²²¹ *Id.* at 21–22 (citing *Sigma-Tau Pharms., Inc. v. Schwetz*, 288 F.3d 141, 146–48 (4th Cir. 2002) (rejecting the argument that § 201.128 requires the FDA to treat common and foreseeable off-label uses as intended uses)).

²²² *Id.* at 22 (citing Temple Decl. ¶ 10).

²²³ *Id.* at 31.

²²⁴ *Id.*

²²⁵ *Id.*

act on its ability to prosecute, and this makes it even more difficult for the government to argue that this system is truly not more broad than necessary. Furthermore, the government's arguments completely skirted the constitutional issue, which was whether the government may restrict a manufacturer's truthful speech on such uses, and force the company to wait to speak until the FDA grants approval of the use.

Although the majority of Allergan's complaint discussed facial claims regarding the constitutionality of the prevailing statutory and regulatory scheme, Allergan also put forth an alternate argument that, at minimum, the prohibitions against their own truthful, non-misleading speech regarding a use for which they were seeking FDA approval were unconstitutional, and particularly incompatible with the fourth prong of *Central Hudson*.²²⁶ As discussed previously, the government's only recognized, substantial interest achieved through these speech restrictions is incentivizing manufacturers to obtain FDA approval for off-label uses. However, if the manufacturer is in the process of seeking approval for the off-label use, the government interest in prohibiting speech about that off-label use no longer directly achieves their stated goal, rendering the restrictions excessively broad.²²⁷

The government's response distinguished between supplemental NDAs as a means and an end.²²⁸ Allergan's argument implies the filing of the request for approval is an end, but instead, it is simply a means to allow the FDA to evaluate the safety and efficacy of the drug.²²⁹ If manufacturers could begin promoting off-label uses directly after filing a supplemental NDA, the effect would be to allow producers to advertise drugs that have not been proven to be safe

²²⁶ Complaint, *supra* note 127, ¶¶ 138–40.

²²⁷ Plaintiff's Motion for Preliminary Injunction, *supra* note 141, at 43.

²²⁸ Defendants' Motion to Dismiss, *supra* note 143, at 39.

²²⁹ *Id.*

and effective, which runs counter to congressional intent in the FD&C Act.²³⁰ Additionally, allowing Allergan and others to promote off-label uses as soon as they filed for FDA approval would incentivize premature, or even facetious, applications, simply to buy some time to promote the uses.²³¹ The government explained that they do, therefore, have an interest in maintaining the current regulatory scheme.

Whether or not restrictions on off-label promotion were sufficiently tailored in situations when the supplemental NDA has already been filed is a legal issue that never saw the inside of a courtroom during the Allergan dispute.²³² On September 1, 2010, the Department of Justice announced a settlement deal with Allergan. As part of the deal, Allergan dropped their First Amendment suit, an aspect of the settlement the DOJ did not mention when they issued a press release announcing the agreement.²³³ The timing of the settlement hints at potential government angst over the effects of the *Citizens United*²³⁴ decision. According to Harvard Law professor Laurence Tribe, during the two decades preceding Allergan's suit, the Supreme Court had been chipping away at earlier decisions limiting commercial free speech.²³⁵ Based on the Court's trend in this area, Professor Tribe believed Allergan had a strong chance at winning in the Supreme Court on a claim that they had a First Amendment right to make truthful, non-misleading statements about off-label uses.²³⁶ Professor Tribe made these comments before the decision in *Citizens United* was handed down, and that decision would have probably lent

²³⁰ *Id.*

²³¹ *Id.* at 40.

²³² Dep't of Justice, Office of Public Affairs, *supra* note 126.

²³³ Thompson Food and Drug Regulation Alerts, Allergan to Pay \$600 Million to Resolve Off-Label Marketing Allegations, Agrees to Drop First Amendment Suit (Sept. 1, 2010), <http://www.thompson.com/public/newsbrief.jsp?cat=FOODDRUG&id=3069>.

²³⁴ 130 S. Ct. 876 (2010).

²³⁵ Sue Reisinger, Let Me Speak! Drug Company Sues in Off-Label Marketing Dispute (Dec. 1, 2009), <http://www.law.com/jsp/cc/PubArticleCC.jsp?id=1202435767811>.

²³⁶ Sue Reisinger, Let Me Speak! Drug Company Sues in Off-Label Marketing Dispute (Dec. 1, 2009), <http://www.law.com/jsp/cc/PubArticleCC.jsp?id=1202435767811>.

additional weight to his prediction. Although *Citizens United* dealt with political speech, not commercial speech,²³⁷ the case powerfully emphasized the historical importance of First Amendment rights, both in general and specific to corporations.²³⁸ The government may have feared a potentially damaging court result from which they would be unable to extricate themselves, as they had been able to do after the WLF litigation a decade earlier, through reinterpreting their guidance documents. The *Citizens United* decision was announced a mere ten days after the government submitted its response to Allergan's complaint, and it may have appeared to the government to be a final harbinger of things to come. Only eight months later, the settlement was announced.

Allergan's argument regarding the unconstitutionality of restricting speech about off-label uses that are pending FDA approval will not go undebated however, as it forms one of the central arguments in the most recent off-label speech case. Although the FDA was able to dodge the issue in the *Washington Legal Foundation* and *Allergan* cases, a recent Second Circuit case, *United States v. Caronia*,²³⁹ may finally force the FDA to confront the First Amendment challenges they have heretofore evaded. *Caronia* differs from *Allergan* in that the defendant is an individual, Alfred Caronia, and not a corporation.²⁴⁰ Mr. Caronia, a sales representative for

²³⁷ 130 S. Ct. at 900.

²³⁸ See *id.* at 896 ("the FEC has created a regime that allows it to select what political speech is safe for public consumption by applying ambiguous tests."); *id.* at 898–99 ("Premised on mistrust of governmental power, the First Amendment stands against attempts to disfavor certain subject or viewpoints . . . Prohibited, too, are restrictions distinguishing among different speakers, allowing speech by some but not others."); *id.* at 900 ("political speech does not lose First Amendment protection 'simply because its source is a corporation'" (citation omitted)); *id.* at 908 ("When Government seeks to use its full power, including the criminal law, to command where a person may get his or her information or what distrusted source he or she may not hear, it uses censorship to control thought. This is unlawful. The First Amendment confirms the freedom to think for ourselves.").

²³⁹ 576 F.Supp.2d 385 (E.D.N.Y. 2008). Oral arguments took place in front of the Second Circuit in December 2010, and an unofficial transcript is circulating on the internet. Posting of Will Sachse, Drug and Device Law Blog, <http://druganddevicelaw.blogspot.com/search?q=caronia> (Jan. 21, 2011, 14:15 EST).

²⁴⁰ Superseding Misdemeanor Information ¶ 5, *United States v. Caronia*, 576 F.Supp.2d 385 (E.D.N.Y. 2008) (No. 06-229).

Orphan Medical, was hired to sell Xyrem, a prescription drug approved to treat two conditions associated with narcolepsy, Excessive Daytime Sleepiness (EDS) and cataplexy.²⁴¹ Based on allegations that he promoted Xyrem to physicians for off-label uses, Mr. Caronia was charged with misbranding and conspiracy to introduce a misbranded drug into interstate commerce.²⁴² In his motion to dismiss, Mr. Caronia contended that the misbranding provisions of the FD&C Act, as applied to him, are an unconstitutional restriction on speech.²⁴³

In response, the government—as they did in the *Washington Legal Foundation* cases—again tried to argue that off-label promotion is conduct, not speech, and thus does not fall under the protection of the First Amendment.²⁴⁴ However, a 2002 Supreme Court case, *Thompson v. Western States Medical Center*,²⁴⁵ held that when pharmaceutical companies advertise compounded drugs²⁴⁶ which can be lawfully sold by pharmacists, but themselves are not FDA approved, this is speech, not conduct.²⁴⁷ Based on this reasoning, the district court believed any argument that Mr. Caronia had engaged in conduct was all but foreclosed.²⁴⁸ Finding that Mr. Caronia had engaged in commercial speech, the court then applied the *Central Hudson* test.²⁴⁹ Concurring with the analysis in *Washington Legal Foundation v. Friedman* regarding prong one, the court agreed that this speech regarded a lawful activity and was not inherently misleading.²⁵⁰ In a cursory analysis, the court also agreed with *Friedman*'s finding of a substantial government

²⁴¹ Superseding Misdemeanor Information, *supra* note 235, ¶¶ 2, 5.

²⁴² *Id.* ¶¶ 3, 17.

²⁴³ *United States v. Caronia*, 576 F.Supp.2d 385, 393 (E.D.N.Y. 2008).

²⁴⁴ *Id.* at 394.

²⁴⁵ 535 U.S. 357 (2002).

²⁴⁶ “Drug compounding is a process by which a pharmacist or doctor combines, mixes, or alters ingredients to create a medication tailored to an individual patient’s needs.” *Id.* at 357.

²⁴⁷ *Id.* at 366.

²⁴⁸ *Caronia*, 576 F.Supp.2d at 395 (citing *Western States Medical Center*, 535 U.S. at 366).

²⁴⁹ *Id.* at 396.

²⁵⁰ *Id.* at 396 (citing *Washington Legal Foundation v. Friedman*, 13 F. Supp. 2d 51, 66–67 (D.D.C. 1998)).

interest, incentivizing pharmaceutical companies to obtain FDA approval for current off-label uses, which was indeed directly served by the speech restrictions.²⁵¹

As in *Friedman*, the main point of contention was whether the government could satisfy the fourth prong of the *Central Hudson* test.²⁵² In addition to depending on the reasoning in *Friedman*, the *Caronia* court also drew inspiration from *United States v. Caputo*,²⁵³ a 2003 district court case that upheld the misbranding provisions in the FD&C Act.²⁵⁴ The Northern District of Illinois found these restrictions to be not more restrictive than necessary, because allowing drug and device manufacturers to put forth any truthful, non-misleading promotional statement about an off-label use would cripple the FDA's ability to evaluate off-label uses for safety and effectiveness.²⁵⁵ The Seventh Circuit ultimately affirmed the lower court's ruling, but on other grounds, and only discussed the constitutional issues in dicta.²⁵⁶ In commenting on the First Amendment implications, the court of appeals discussed the case in the context of the Supreme Court's decision in the previous year in *Western States*. *Western States* invalidated portions of the FD&C Act, as amended by FDAMA, as unconstitutional restrictions on commercial speech.²⁵⁷ The voided portions would have allowed pharmacies to advertise their compounding services, but prohibited them from promoting any particular compounded drugs, unless they first sought FDA approval.²⁵⁸ The FDA was concerned that large-scale production of compounded drugs, which are exempt from the FDA "new drug" requirements, would allow pharmacists to evade the FDA's system for ensuring safety and efficacy of products on the

²⁵¹ *Id.* at 396–98 (citing *Friedman*, 13 F. Supp.2d at 69–72).

²⁵² *Id.* at 398.

²⁵³ 288 F.Supp.2d 912 (N.D. Ill. 2003).

²⁵⁴ *Caronia*, 576 F.Supp.2d at 399.

²⁵⁵ *Id.* at 399 (citing *Caputo*, 288 F.Supp.2d at 919).

²⁵⁶ *Id.* at 399–400 (citing *Caputo*, 288 F.Supp.2d at 940).

²⁵⁷ *Thompson v. Western States Medical Center*, 535 U.S. 357, 360 (2002).

²⁵⁸ *Id.* at 364–65.

market. Advertising, then, was a proxy for large-scale operations: if a pharmacy compounded such a small amount of drugs that they did not advertise their product, then it was assumed the testing requirements would be completely unfeasible to implement. Thus the pharmacy would be allowed to continue to skirt the FDA's requirements. If a pharmacy produced such a large quantity of compounded drugs that they wished to advertise their creation, this implied testing was feasible, and so the FDA would subject them to the approval process.²⁵⁹

The Supreme Court struck down this policy under *Central Hudson* analysis, explaining that the government had failed to show that their restriction was not more expansive than necessary to achieve their goal.²⁶⁰ The Court chastised the government for failing to explore alternate means of reaching their objectives, emphasizing that “regulating speech must be a last—not first—resort.”²⁶¹ The very presence of multiple other, less restrictive means in this situation indicated the government was overstepping its bounds.²⁶² According to the Seventh Circuit's interpretation of *Western States*, the Supreme Court did indicate that some restrictions placed on drug makers from disseminating truthful, non-misleading statements about their product's off-label uses are unconstitutional.²⁶³ The boundaries between acceptable and unacceptable, however, were undefined, and the Seventh Circuit implied that courts, in creating the distinction, should reflect upon consequentialist policy considerations.²⁶⁴ On the one hand, manufacturers have the most information about off-label uses, and if such practices are common and will be discussed by others, then it makes sense not to single out the party with the most

²⁵⁹ *Id.* at 370–71.

²⁶⁰ *Id.* at 371.

²⁶¹ *Id.* at 373.

²⁶² *Id.* at 371–72 (citing *Rubin v. Coors Brewing Co.*, 514 U.S. 476 (1995)).

²⁶³ *United States v. Caronia*, 576 F.Supp.2d 385, 400 (E.D.N.Y. 2008) (citing *United States v. Caputo*, 288 F.Supp.2d 912, 939 (N.D. Ill. 2003)).

²⁶⁴ *See Caronia*, 576 F.Supp.2d at 400 (citing *Caputo*, 288 F.Supp.2d at 912).

information and bar him from speaking.²⁶⁵ On the other hand, allowing the off-label speech at issue could cause the FDA to withhold approval for drugs or devices that have common, but under-analyzed, off-label uses, harming consumers by decreasing their options.²⁶⁶ The district court made clear that they recognized Caronia’s case “demands answers to the questions raised but not resolved by the Seventh Circuit in *Caputo*.”²⁶⁷

The district court felt confident in distinguishing the prohibitions Caronia was challenging from those struck down in *Western States*. The government in *Western States* had been unable to show that the speech restriction was truly necessary, and more than a mere convenient mechanism to achieve their goal.²⁶⁸ In contrast, “the FDA’s maintaining through the FDCA’s misbranding provisions *some* control over the off-label promotion of manufacturers does appear essential to maintaining the integrity of the FDA’s new drug approval process,” and thus passed the fourth prong of *Central Hudson*.²⁶⁹ The court’s conclusion was buttressed by the perceived lack of non-speech restrictions that could still functionally operate to prevent manufacturers from being able to completely skirt the FDA approval process.²⁷⁰

The Eastern District of New York then denied Mr. Caronia’s motion to dismiss, and less than two months later, a jury found him guilty of conspiracy to introduce a misbranded drug into interstate commerce.²⁷¹ He was sentenced to one year of probation, one hundred hours of community service, and a \$25 fine.²⁷² Mr. Caronia appealed the case, both on procedural issues and the First Amendment claim. Conceding that the first three prongs of *Central Hudson* were

²⁶⁵ *Id.* (citing *Caputo*, 288 F.Supp.2d at 939–40).

²⁶⁶ *Id.* (citing *Caputo*, 288 F.Supp.2d at 939–40).

²⁶⁷ *Id.* at 401.

²⁶⁸ *Id.*

²⁶⁹ *Id.*

²⁷⁰ *Id.*

²⁷¹ Verdict Sheet, *United States v. Caronia*, 576 F.Supp.2d 385 (E.D.N.Y. 2008) (No. 06-229).

²⁷² Brief and Appendix for Defendant-Appellant at 1, *United States v. Caronia*, No. 09-5006 (2d Cir. Apr. 16, 2010) [hereinafter Brief for Defendant].

met, Mr. Caronia focused on arguing that the restriction was overly broad.²⁷³ A narrower rule suggested by the appellant was that the FDA could prohibit truthful, non-misleading speech about off-label uses only if those off-label uses are currently not pending FDA approval.²⁷⁴ In this way, the government could still achieve its objective of incentivizing manufacturers to get uses on-label, without unduly burdening commercial speech or corrupting the integrity of the FDA approval process.²⁷⁵

On appeal, Mr. Caronia received eloquent and effective support on his First Amendment claims from the Washington Legal Foundation. Although the Second Circuit initially indicated they would decide the case without hearing oral arguments, after receiving the WLF's amicus brief, they agreed to hear from the parties, as well as the WLF.²⁷⁶ In their brief, the WLF first focused on the government's contention that this regulatory scheme bans conduct, and not promotional speech, because the speech is merely used as evidence of intent to engage in prohibited conduct.²⁷⁷ Criticizing this argument as "semantic gamesmanship," the WLF pointed out that *Western States* dealt with an analogous situation, yet the government in that case admitted they were regulating speech.²⁷⁸ The relevant statute in *Western States* indirectly regulated speech in that a compounded drug became an unapproved "new drug" only if the pharmacy advertised or promoted the compound.²⁷⁹ Thus, speech in *Western States* was used to determine whether a violation of the law was being committed, just as it is being used to determine a violation in off-label promotion cases such as Mr. Caronia's.²⁸⁰ By finding that the

²⁷³ *Id.* at 38.

²⁷⁴ *Id.*

²⁷⁵ *Id.* at 38–40.

²⁷⁶ Post of Rich Samp to Forbes On the Docket, <http://blogs.forbes.com/docket/> (Dec. 1, 2010, 20:05 EST).

²⁷⁷ Brief for Washington Legal Foundation as Amicus Curiae Supporting Appellant at 12, *United States v. Caronia*, No. 09-5006 (2d Cir. Apr. 16, 2010) [hereinafter WLF Amicus Brief].

²⁷⁸ *Id.* at 12–13 (citing *Thompson v. Western States Medical Center*, 535 U.S. 357, 366 (2002)).

²⁷⁹ *Id.* at 12.

²⁸⁰ *Id.* at 13.

analogous speech restrictions in *Western States* were unconstitutional, the WLF asserts that the Supreme Court established a rule that “the First Amendment governs laws that use speech as the *determining factor* over whether conduct is unlawful just as fully as a direct prohibition on speech,” and thus in *Caronia*, the government had no legitimate claim of regulating conduct.²⁸¹

The WLF also drew support from the Supreme Court’s recent decisions in *Citizens United v. Federal Election Comm’n*²⁸² and *Greater New Orleans Board Ass’n v. United States*²⁸³ (GNOBA) regarding speech restrictions resting on speaker-based distinctions.²⁸⁴ The current regime allows doctors to speak to patients about off-label uses, but pharmaceutical companies and their employees (including physicians) are unable to speak to physicians about off-label uses.²⁸⁵ Yet in *GNOBA*, the Supreme Court cautioned that “decisions that select among speakers conveying virtually identical messages are in serious tension with the principles undergirding the First Amendment,”²⁸⁶ and reiterated this message in *Citizens United* as well.²⁸⁷

The final argument the WLF focused on in their brief was *Central Hudson*’s fourth requirement that speech restrictions be proportionally tailored to the ends sought by the government. While the WLF acknowledged that the governmental interest in incentivizing supplemental NDAs was a legitimate one, the speech restrictions failed to be narrowly tailored to this objective, because the government could have restricted less speech, or in the alternative, conduct.²⁸⁸ WLF put forth several possible options the government could have considered.²⁸⁹

²⁸¹ *Id.*

²⁸² 130 S. Ct. 876 (2010).

²⁸³ 527 U.S. 173 (1999).

²⁸⁴ WLF Amicus Brief, *supra* note 272, at 20.

²⁸⁵ *Id.* at 19.

²⁸⁶ *Id.* at 6 (citing *Greater New Orleans Board Ass’n*, 527 U.S. at 194).

²⁸⁷ *Citizens United*, 130 S. Ct. at 898 (explaining that “restrictions distinguishing among different speakers, allowing speech by some but not others,” is “prohibited” by the First Amendment).

²⁸⁸ WLF Amicus Brief, *supra* note 272, at 26.

²⁸⁹ WLF Amicus Brief, *supra* note 272, at 26–30.

On December 2, 2010, Judges Chin, Raggi, and Livingston of the Second Circuit heard oral arguments on *United States v. Caronia*.²⁹⁰ The bench focused primarily on the First Amendment issues presented.²⁹¹ Judge Raggi pressed the WLF representative, Eric Murphy, on the fact that the fourth prong is not a least restrictive means test, but rather an issue of proportionality.²⁹² Murphy was able to respond by alluding to favorable language from *Western States*,²⁹³ in which the Court cautioned that “if the Government could achieve its interest in a manner that does not restrict speech, or that restricts less speech, the Government must do so.”²⁹⁴ By stating that the government must “restrict[] less speech” if possible, the Supreme Court seemed to be modifying *Central Hudson* to imply that a proportionality analysis does entail an examination of least restrictive means. utilize

The bench seemed to question the government’s representative, Douglas Letter, more intensely. Mr. Letter started by emphasizing that the government was restricting conduct, not speech, and that promotion of off-label use was merely employed as evidence of intent to introduce misbranded drugs (in other words, drugs lacking instructions for adequate use) into interstate commerce.²⁹⁵ According to the government, it is the FDA’s policy that if drug manufacturers engage in certain speech, it will be taken as evidence of their intent, but in and of itself the speech about off-label uses is not a crime.²⁹⁶ The judges seemed skeptical of this claim. Judge Livingston posed a hypothetical: if a drug manufacturer received a call from a pharmacy asking for a delivery of drugs in order to fill a substantial amount of off-label prescription

²⁹⁰ SECOND CIRCUIT COURT OF APPEALS, APPROVED CALENDAR 3 (Nov. 17, 2010), *available at* <http://www.ca2.uscourts.gov/Docs/Calendar/nov/nov29.pdf>.

²⁹¹ Unofficial Transcript of Oral Argument at 2–15, *United States v. Caronia*, No. 09-5006 (2d Cir. Dec. 2, 2010).

²⁹² *Id.* at 3–5.

²⁹³ *Id.* at 5.

²⁹⁴ *Thompson v. Western States Medical Center*, 535 U.S. 357, 371 (2002).

²⁹⁵ Unofficial Transcript of Oral Argument, *supra* note 286, at 6–10.

²⁹⁶ *Id.* at 12.

requests from physicians, would the drug manufacturer, in making the sale, exhibit intent to introduce misbranded drugs into interstate commerce, thus opening himself up to the same type of liability at issue in this case?²⁹⁷ The government responded that the drug manufacturer would not be liable, because it would be exhibiting “subjective intent,” which is different than the “objective intent” the government discerns from promotional speech.²⁹⁸ Although Judge Livingstone then pressed Mr. Letter for more examples of the distinction between subjective and objective intent, Mr. Letter did not give any additional clarity. Judge Raggi asked whether this crime had ever been proven without promotional speech by the defendant, and Mr. Letter admitted he was unaware of any such case.²⁹⁹

The rest of the bench’s questions for the government probed whether less restrictive means existed to protect the integrity of the supplemental NDA process.³⁰⁰ Judge Raggi asked Mr. Letter whether it would be acceptable to the FDA if the regulatory regime allowed manufacturers to discuss off-label uses only if those uses were currently pending approval before the FDA.³⁰¹ Once the application was filed, manufacturers could be permitted to speak about off-label uses, but only during a restricted time period, in order to prevent needless delays in filing required documents, designed only to lengthen the amount of time the applicants had to speak about off-label uses.³⁰² Judge Raggi, tipping her hand that she still did not buy the government’s argument that they weren’t prohibiting speech, stated that such a regime may be preferable to one that “completely preclude[s] speech.”³⁰³

²⁹⁷ *Id.* at 9–10.

²⁹⁸ *Id.* at 11.

²⁹⁹ *Id.* at 10.

³⁰⁰ *Id.* at 12–14.

³⁰¹ *Id.* at 12–13.

³⁰² *Id.* at 13.

³⁰³ See *id.*

Mr. Letter quickly corrected the judge by reminding her of the government's position that they weren't restricting speech, and then argued that such a regime would be unacceptable because it would expose the public to unsubstantiated claims during the approval process, which often takes years to complete.³⁰⁴ Citing tragic public health disasters resulting from prescriptions for off-label uses that were perceived by the medical community to be safe, but caused serious side effects among users, the government portrayed Judge Raggi's suggested regulatory regime as one that would be uncontrollable. Judge Raggi, undeterred, suggested the government could quickly halt sales of drugs for off-label uses if such a problem came up, and that the dangers of such situations occurring were outweighed by the value of having more speech in the marketplace.³⁰⁵ Mr. Letter responded by portraying the government's position as one that also strove to provide more speech in the marketplace: by channeling more drugs through the approval process, doctors would have access to more information on a drug's safety and efficacy.³⁰⁶

The Second Circuit's decision could instigate real change in the FDA regulatory scheme of off-label promotion. Given the bench's skepticism towards the government's position during oral arguments, it would not be surprising if the Second Circuit concluded that under *Central Hudson*, restrictions on commercial speech regarding off-label uses are overly broad when the manufacturer has already applied for a supplemental NDA. Because Mr. Caronia's as-applied challenge focuses only on manufacturers with pending supplemental NDAs, a decision in the appellant's favor would yield permission to speak in only a relatively narrow range of situations. But such an outcome would still trigger new FDA regulations and thus—hopefully—clear areas of acceptable behavior. This stands in stark contrast to the FDA's current guidance, which

³⁰⁴ *Id.*

³⁰⁵ *Id.* at 13–14.

³⁰⁶ *Id.* at 14.

purports to create safe harbors for manufacturers, but is ultimately not binding on the FDA. The decision could propel the FDA toward greater clarity in other areas of their regulatory regime as well.

Given the current ambiguity, rooted in the FDA's back-pedaling during the WLF litigation, such changes may reap benefits to society at large. When the rules are clearer and offer pharmaceutical companies a bit more leeway to speak about emerging new uses, these producers may violate the regulations less. As a result, taxpayer-funded enforcement efforts would decrease, and drug companies would no longer need to pass on these costs of regulatory compliance to consumers. Individuals and groups that criticized the FDA for its January 2009 guidance document³⁰⁷ would strenuously object to any expanded ability to discuss off-label uses, and finding a way to appease these advocacy groups will make for a smoother transition. The FDA may also need to get creative in crafting regulations that will diminish the incentives for manufacturers to rush in a supplemental NDA, in order to prevent abuse. For example, companies could use the intervening time to heavily advertise an off-label use, banking on the fact that, regardless of whether they ultimately can prove safety and efficacy to the FDA, doctors may become accustomed to prescribing the drug off-label. While there are legitimate dangers that manufacturers may exploit this exercise of First Amendment rights, the theme that emerged at the end of the *Caronia* oral arguments in the Second Circuit—that more speech is generally better—seems accurate here. Drug companies do a tremendous amount of research, and often hire top experts in the field to discuss their products. Muzzling these actors, who know more about their product than anyone else in the market, seems to be an inappropriately blunt

³⁰⁷ See, e.g., Letter from Henry Waxman, Chairman of House Comm. on Oversight and Gov't Reform, to Andrew Eschenbach, Comm'r of U.S. Food and Drug Admin. (Nov. 30, 2007), available at http://www.fdalawblog.net/fda_law_blog_hyman_phelps/files/waxman_letter.pdf; PUBLIC CITIZEN, COMMENTS ON DRAFT GUIDANCE FOR INDUSTRY ON OFF-LABEL PROMOTION OF DRUGS AND MEDICAL DEVICES (2008), available at <http://www.citizen.org/hrg1838>.

approach. The FDA can promulgate regulations to create a more nuanced system that still aligns manufacturer incentives with patient safety, and harnesses their speech to move beneficial therapies from producers to consumers.